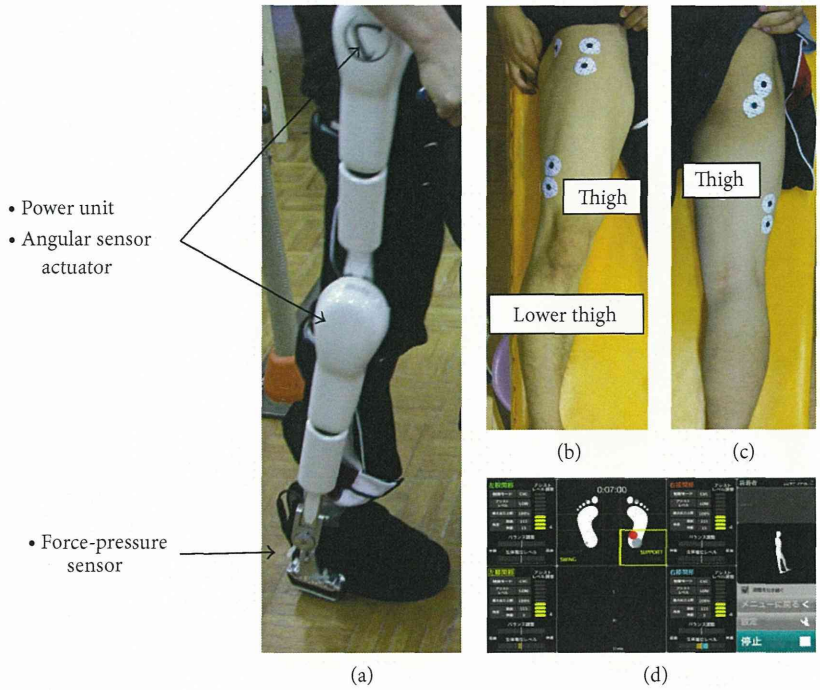

FIGURE 1: Newly-developed wearable robot suit, hybrid assistive limb (HAL). The HAL suit has power units and force-pressure sensors in the shoes. The power units consist of angular sensors and actuators on bilateral hip and knee joints (a). Muscle action potentials are detected through the electrodes on the anterior and posterior surface of the thigh ((b), (c)). Assist levels and force-pressure are shown on a computer monitor (d).

sensors and actuators on the bilateral hip and knee joints (Figure 1). The HAL suit can support the wearer's motion by adjusting the level and timing of assistance [7]. HAL training, using muscle activity, has the potential to intensify the feedback by evoking by an appropriate motion more strongly than standard robot training [9]. HAL training has been shown to improve gait speed or cadence for chronic stroke and incomplete spinal cord injury [8, 9]. However, no studies have attempted to clarify the feasibility of rehabilitation with HAL for patients with residual paralysis after spinal decompression for thoracic OPLL or OLF.

This case was markedly improved locomotor function by training with HAL, although recovery did not start until 7 weeks after spinal decompression of thoracic OPLL. Therefore, we report a case of patient-assistive HAL walking rehabilitation from an early stage for facilitating locomotor functions for patients with severe residual paralysis.

2. Case Presentation

A 60-year-old woman (body mass index: 31.1 kg/m^2) presented with onset of pain and numbness in her right lower limb and gait disturbance. The diagnosis was cervico-thoracic OPLL. After 15 months, her symptoms had gradually progressed, showing motor and sensory paresis of the lower limb and urinary disturbance. Magnetic resonance imaging showed areas of OPLL extending from T2 to T8 and T9/T10 OYL (Figure 2). Because of progressive myelopathy, she underwent posterior decompression surgery two times. However, she showed aggravation of myelopathy after the second surgery, complete motor and sensory paralysis below T4, and urinary retention. She then underwent anterior decompression surgery to remove the OPLL. Active movement of her toes was weak at 1 day after surgery. She underwent physical therapy (PT) with pharmacological and high atmospheric pressure oxygen inhalation therapy. However, her motor and

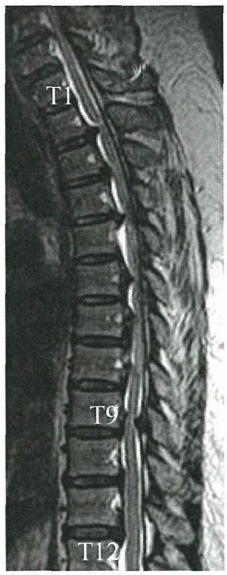

FIGURE 2: T1-weighted magnetic resonance imaging showed areas of OPLL extending from T2 to T8 and T9/T10 OYL.

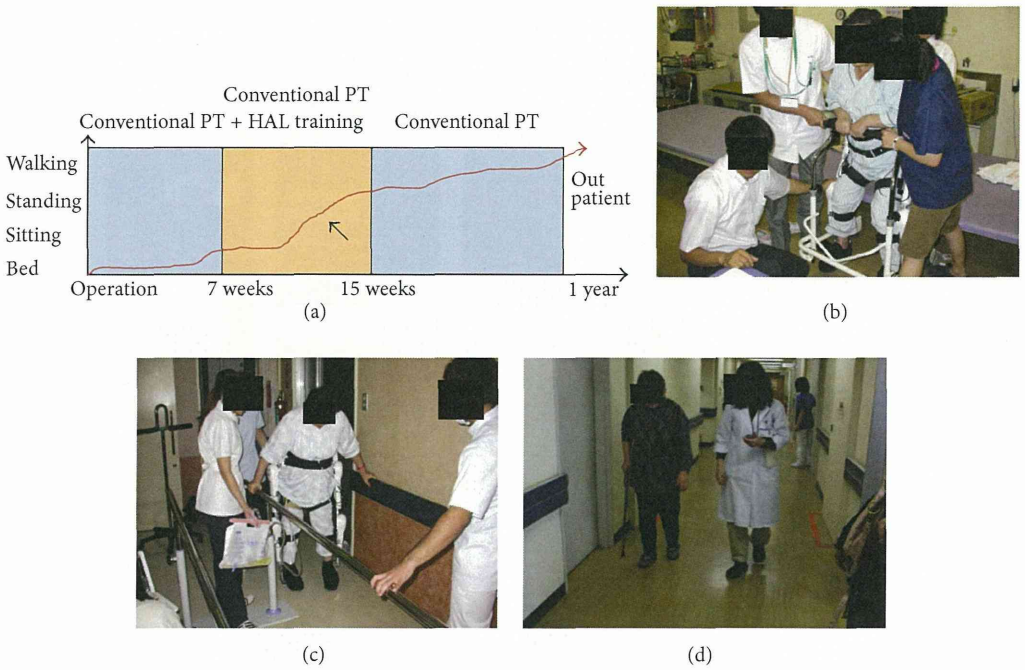

FIGURE 3: Improvement time course of activity of the patient in a schematic view (a). Although she underwent conventional physical therapy (PT), she was still bedridden 7 weeks after surgery. Locomotor functions of the patient improved considerably by intervention of the robot suit hybrid assistive limb (HAL) training. Subsequently, the walking ability recovered rapidly (arrow). When she put on the HAL at baseline, she could stand for only few seconds with assistance from three tree therapists (b). However, she could walk in the parallel bars at 12 weeks after surgery (c) and could walk independently 1 year after surgery (d).

sensory paralyses did not improve. She was still bedridden 7 weeks after surgery and at risk of disuse syndrome. We decided to use HAL in addition to the conventional PT such as muscle strength exercises and range of motion exercises. Before participating in walking exercise using HAL, the subject provided informed consent, and the study was approved by the Ethics Committee of the Kagoshima University Faculty of Medicine.

Clinical assessments were carried out at the initial evaluation (at 7 weeks after final surgery) and 8 weeks and 8 months after HAL intervention (15 weeks and 1 year after surgery, resp., Table 1). After the initial evaluation, the subject underwent 6 HAL sessions of 70 minutes per week for 8 weeks. Sessions consisted of a standing and sitting exercise, and walking on the ground with HAL. Standing and walking training started in parallel bars with HAL. A typical 70-minute HAL training session proceeded as follows: preparation of electrodes, putting on the HAL suit, and computer setup (15 min); HAL training (40 min, including rest time); taking off the HAL suit and electrodes (15 min). Three therapists implemented the training. The HAL suit has a hybrid control system comprising the CVC and CAC. The CVC mode of the HAL suit can support the patient's voluntary motion according to the voluntary muscle activity and the assistive torque provided to each joint [9]. This study used the CVC mode, which allows the operator to adjust the degree of physical support to the patient's comfort and gradually reduce support as training progresses. After the end of HAL intervention, the patient underwent conventional PT without HAL in another hospital, and she was discharged 10 months after surgery.

TABLE 1: Baseline and clinical assessment during follow-up period.

	7 weeks (baseline)	15 weeks (end of HAL)	After 1 year
MMT (U/L)	5/1-2	5/3-4	$5/4^{+}$-5
JOA score	8	11	13
ASIA classification	C	D	D
ASIA score (lower limbs)	23	34	42
WISCI II	0	8	20
FIM motor score	22	40	83

MMT: Manual muscle testing. JOA: Japan orthopedic association (maximum score: 17). ASIA: American spinal injury association. WISCI: Walking index for spinal cord injury (score range 0 to 20). FIM: Functional independence measure (maximum score: 91).

Locomotor functions of the patient improved considerably by the intervention of HAL training. Subsequently, her walking ability recovered rapidly and she was able to walk independently six months after surgery. Figure 3 shows the improvement time course of activity of the patient in a schematic view. At 15 weeks after surgery, she was able to sit without back support and transfer to a wheelchair independently. She could walk in parallel bars without HAL, although rocking of the knee was observed while standing. At 1 year

after surgery, she was able to walk independently with a T-cane.

3. Discussion

This case report describes the feasibility of facilitating locomotor functions with HAL training for patients with residual paralysis after spinal surgery. Matsumoto et al. [10] reported improvement in 36.8% of patients but deterioration in 8.4% after spinal surgery for thoracic OPLL in a retrospective multicenter study of 154 Japanese hospitals. The present patient was operated on 3 times and showed aggravation of her lower limb myelopathy after surgery. Although recovery did not start until 7 weeks after surgery, her locomotor function markedly improved by combining training with HAL, suggesting that HAL training facilitated recovery of locomotor functions. The HAL may facilitate rehabilitation by providing postural support and assisted voluntary muscle activity during ambulation.

HAL is a robotic device with potential rehabilitation applications that are dependent on the physical support it can provide [9]. A patient's recovery of locomotor functions may be due to changes in plasticity of the spinal cord and supraspinal centers. Appropriate sensory inputs, such as maximum weight loading, facilitating proper trunk posture, and hip extension, are essential for maximizing functional recovery [11]. Sensory input evoked HAL-induced motion may affect the central nervous system, resulting in recovery of locomotor functions. Furthermore, the visual feedback of watching a display indicating the center of gravity and range of motion of the lower limbs may also affect the central nervous system. HAL rehabilitation can be implemented safely and effectively for early mobilization and gait training for patients with residual paralysis after spinal surgery.

This study had a clear limitation in that the HAL training was started relatively soon after surgery. However, even if this patient was still in the recovery period, her locomotor function markedly improved by combining training with HAL. HAL training at an early stage may be necessary to prevent disuse syndrome such as muscle weakness in the lower limbs or joint contracture. The subject may also have experienced improved motivation for rehabilitation by HAL training use from an early stage, because she had been bedridden for 7 weeks after surgery. The findings from this case report suggest that HAL training for voluntary control of leg joint motion from an early phase is a safe and effective option for restoring locomotor functions in patients with residual paralysis after spinal surgery.

4. Conclusion

We concluded that for patients of thoracic OPLL, the early HAL training with physiotherapy may enhance motor recovery after surgery. Early mobilization using HAL may be also advocated to prevent post surgery complications, such as contractures and deep vein thrombosis.

Conflict of Interests

The authors have no competing financial interest to declare.

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RESEARCH LETTER

AMERICAN JOURNAL OF medical genetics PA

FOP in China and Japan: An Overview From Domestic Literatures

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TO THE EDITOR:

FOP is an autosomal dominant disorder, characterized by progressive ectopic ossification leading to devastating physical disabilities and malformation of the great toe and occasionally of the thumb. It is known that an activating mutation of *ACVR1* is responsible for FOP. FOP is a rare disorder with incidence of 1/2,000,000 [Connor and Evans, 1982a,b]. China has a population of more than 1.3 billion, and Japan has about 0.13 billion people. Although the FOP case reports published in China and Japan might provide valuable information for this rare disease considering their large populations, most cases were published in medical journals of their own respective languages. In order to obtain the information of FOP patients reported in Chinese and Japanese, we summarized the FOP case reports published in China and Japan and analyzed the similarities and differences of the Chinese and Japanese patients to compare their characteristics with those of reports published in international journals.

Literature search was made by using relevant key words in three Chinese and one Japanese electronic databases (Fig. 1). The case reports on FOP published in Chinese or Japanese were included in this research. All references of the identified articles were screened and the relevant articles were also retrieved (see Supporting Information online). Similar case reports were confirmed by telephone to the original author and duplicate publications were excluded.

A total of 86 Chinese patients (46 males and 40 females) and 41 Japanese patients (21 males and 20 females) were included. The median age of onset was defined as the age of first flare-up leading to heterotopic ossification. The clinical information of all patients including age of onset, age of diagnosis, site of heterotopic ossification, malformation, and interventions were extracted (Table I). A total of 32% Chinese and 83% Japanese patients were reported as having spinal deformities such as scoliosis, lordosis, or kyphosis. Unfortunately, 11 Chinese and 19 Japanese patients underwent surgical intervention, but the percentage of patients who underwent surgeries decreased in recent 10 years for both Chinese and Japanese patients. Medical intervention included administration of steroid hormones, non-steroidal anti-inflammatory drugs (including cyclooxygenase-2 inhibitor drugs), and diphosphonates-EHDP.

It was reported in earlier articles that almost all FOP patients had characteristic malformations of the great toes [Connor and Evans, 1982a,b; Kitterman et al., 2005; Janati et al., 2007]. However in several recent studies, normal great toes and late onset heterotopic ossification were reported with patients with FOP variants [Bocciardi et al., 2009; Kaplan et al., 2009; Barnett et al., 2011]. The classic FOP (with the characteristic features of great toe malformations and progressive heterotopic ossification), FOP-plus (classic defining features of FOP plus one or more atypical features) and FOP variants (major variations in one or both of the two classic defining features of FOP) were reported as having different types of *ACVR1* mutation which showed correlations with the age of onset of heterotopic ossification or malformations [Kaplan et al., 2009]. In this study, 7% of the Chinese patients and 2% of the Japanese patients were reported as having normal toes. In a previous research, 59% of FOP patients were reported as having malformed thumbs [Connor and Evans, 1982a,b]. While in this study, only 21% of the Chinese and 12% of the Japanese patients were reported as having malformed thumb. Because the exact

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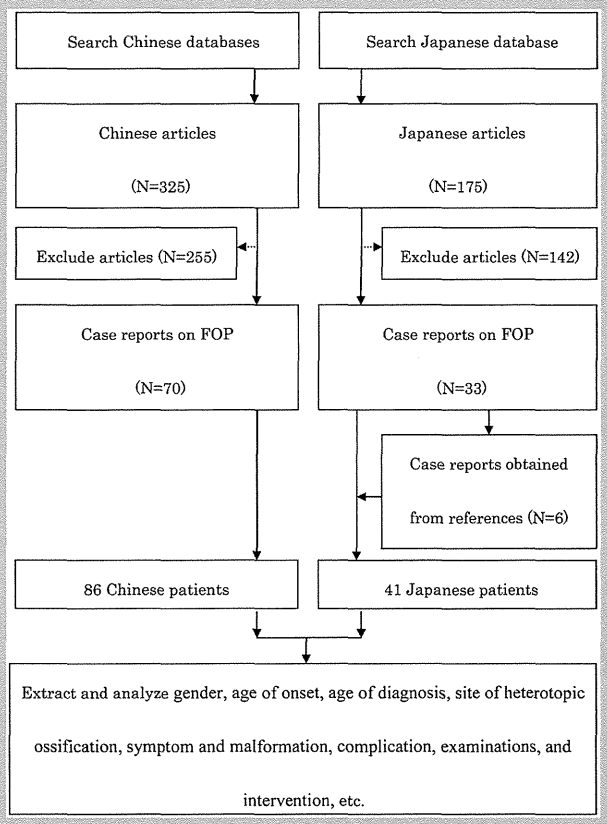

FIG. 1. Three Chinese electronic databases, including China National Knowledge Infrastructure (CNKI), Chinese Scientific Journal Databases (VIP), and Wanfang data were searched with the terms "jin xing xing gu hua xing xian wei fa yu bu liang (fibrodysplasis ossificans progressiva, FOP)" and "jin xing xing gu hua xing ji yan (myositis ossificans progressiva, MOP)" in the full text. The Japanese electronic database, Ichushi WEB, was searched with the terms "sinkousei kokkasei seniikeiseisyou (FOP)," "sinkousei kokkasei kin'en (MOP)," "sinkousei kakotusei kin'en (MOP)," "fibrodysplasis ossificans progressiva," and "myositis ossificans progressiva" in full text. After exclusion of duplicate case reports and addition of reports obtained from references, 86 Chinese and 41 Japanese patients remained for analyses.

TABLE I. Contrast of Chinese and Japanese Patients With FOP

	Chinese	Japanese
Age of onset (year): median (range)*	3.0 (0–38)	3.0 (0–16)
Age of diagnosis (year): median (range)**	10.5 (0–53)	7.0 (0–27)
Site of heterotopic ossification (%)		
At onset	Neck (30) > trunk (27) > head (13)	Neck (42) > trunk (24) > head (17)
When reported	Trunk (94) > neck (64) > shoulder (62)	Trunk (85) > neck (76) > shoulder (71)
Great toe (%): Mal/nor/no info[a]	51/7/42	73/2/24
Thumb (%): Mal/nor/no info[a]	21/9/72	12/5/83

[a]Mal/nor/no info stands for malformation/normal/no information.
*By Kolmogorov–Smirnov nonparametric test, $P = 0.532$, grand median = 3.0.
**By Kolmogorov–Smirnov nonparametric test, $P = 0.027$, grand median = 9.0.

reason for less reported percentage of malformed great toe and thumb is unknown, the ethical or racial differences of FOP subtypes and the *ACVR1* mutations with their genotype–phenotype should also be explored in future research.

Common anomalies associated with FOP such as short, broad femoral necks and metaphysical widening [Deirmengian et al., 2008] or typical complications such as baldness [Connor and Evans, 1982a,b] were not reported in these Chinese and Japanese reports. The fact may be attributed to selection-bias, because earlier reports might come from orthopedic surgeons. Lack of long-term follow up may have precluded identification of these rare onset associations.

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CLINICAL REPORT

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ACVR1 (587T>C) Mutation in a Variant Form of Fibrodysplasia Ossificans Progressiva: Second Report

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Fibrodysplasia ossificans progressiva (FOP) is a rare, congenital disorder caused by heterozygous mutation of the bone morphogenetic protein type I receptor *ACVR1*. Various forms of atypical FOP have recently been identified, and a novel mutation, *ACVR1* (587T>C), was reported in 2011. We report on the second patient worldwide with *ACVR1* (587T>C) mutation. A 22-year-old Japanese male with no family history of heterotopic ossification did not show any malformation of the great toes and showed normal development from birth to the age of 17 years, when heterotopic ossification appeared in the lumbar area. The clinical symptoms were similar to those reported previously: the delayed onset with a slower and mild clinical course and little finger camptodactyly. Gene analysis revealed that the patient was heterozygous for *ACVR1* (587T>C) mutation, the same one as reported in 2011, suggesting a correlation between the location of the mutation and the clinical symptoms. This second report of *ACVR1* (587T>C) mutation worldwide is particularly meaningful in that it highlights the difference between clinical symptoms of the first reported patient with *ACVR1* (587T>C) mutation and those of classic FOP.

Key words: fibrodysplasia ossificans progressiva (FOP); FOP variant; slower and mild clinical course; rare mutation *ACVR1* (587T>C); activin A type 1 receptor gene (*ACVR1*); bone morphogenetic protein (BMP)

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INTRODUCTION

Fibrodysplasia ossificans progressiva (FOP) (OMIM 135100) is a rare, congenital disorder manifesting progressive heterotopic ossification and congenital malformation of great toes. Periarticular heterotopic ossification in the extremities causes restricted range of joint motion, joint ankylosis and disturbances in the activities of daily living, particularly gait. In addition, if heterotopic ossification appears in the spine or thoracic area, trunk deformity and respiratory disorders may develop and vital prognosis may be threatened. The movement of jaw muscles deteriorates causing trismus. In general, heterotopic ossification first occurs during infancy and later childhood, following subcutaneous swelling and sclerosis called flare-ups. Flare-ups are sometimes triggered by invasive wounds such as bruising, injury, and surgery.

The genes responsible for FOP have been investigated, and results of sequence analysis on 32 sporadic and 5 familial cases identified the same mutation (617G>A) in *ACVR1* in both groups [Shore et al., 2006]. *ACVR1* encodes for the protein receptor ALK2, which functions as a receptor of a factor called BMP that binds to the ALK2 receptor and is largely contained in the bones. BMP is believed to function in the regeneration of bone tissue. Furthermore BMP is involved in ectopic bone formation by influencing the surrounding cells. The first mutation of the ALK2 receptor found in an FOP patient was the R206H mutation, which revealed that the mutation causes activation of the receptor.

Atypical forms of FOP have been identified, and 10 point mutations in *ACVR1* have been reported to date [Smith et al., 1976; Connor and Evans, 1982; Lin et al., 2006; Shore et al., 2006; Nakajima et al., 2007; Furuya et al., 2008; Bocciardi et al., 2009; Kaplan et al., 2009; Lee et al., 2009; Petrie et al., 2009; Carvalho et al., 2010; Ratbi et al., 2010]. In 2011, a novel mutation *ACVR1* (587T>C) was reported [Gregson et al., 2011]. We report

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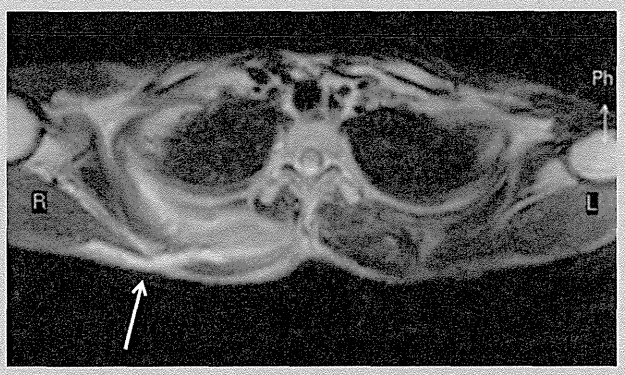

FIG. 1. MRI taken when difficulty in right shoulder elevation occurred. MRI shows a T2-high intensity lesion in the right scapular region (subcutis to tunica muscularis, arrow).

the results and analysis of the second patient of *ACVR1* (587T>C) mutation worldwide. This case report was approved by the Ethics Committee of the Faculty of Medicine, the University of Tokyo with the patient's written consent.

CLINICAL REPORT

A 22-year-old Japanese male patient with no family history of heterotopic ossification, normal development since birth, and no limited range of motion of joints or trunk until 16 years of age visited our department. At 17 years, he fell from an elevation of 1–2 m and bruised his back. An X-ray taken 1 week later showed no sign of heterotopic ossification or soft tissue swelling; however, a few months later, a follow-up X-ray and magnetic resonance imaging (MRI) revealed heterotopic ossification in the lumbar area. Later, he had an episode of flare-up and fracture of the lumbar heterotopic ossification subsequent to running and was unable to stand. At 19 years, decreased range of motion in his right shoulder

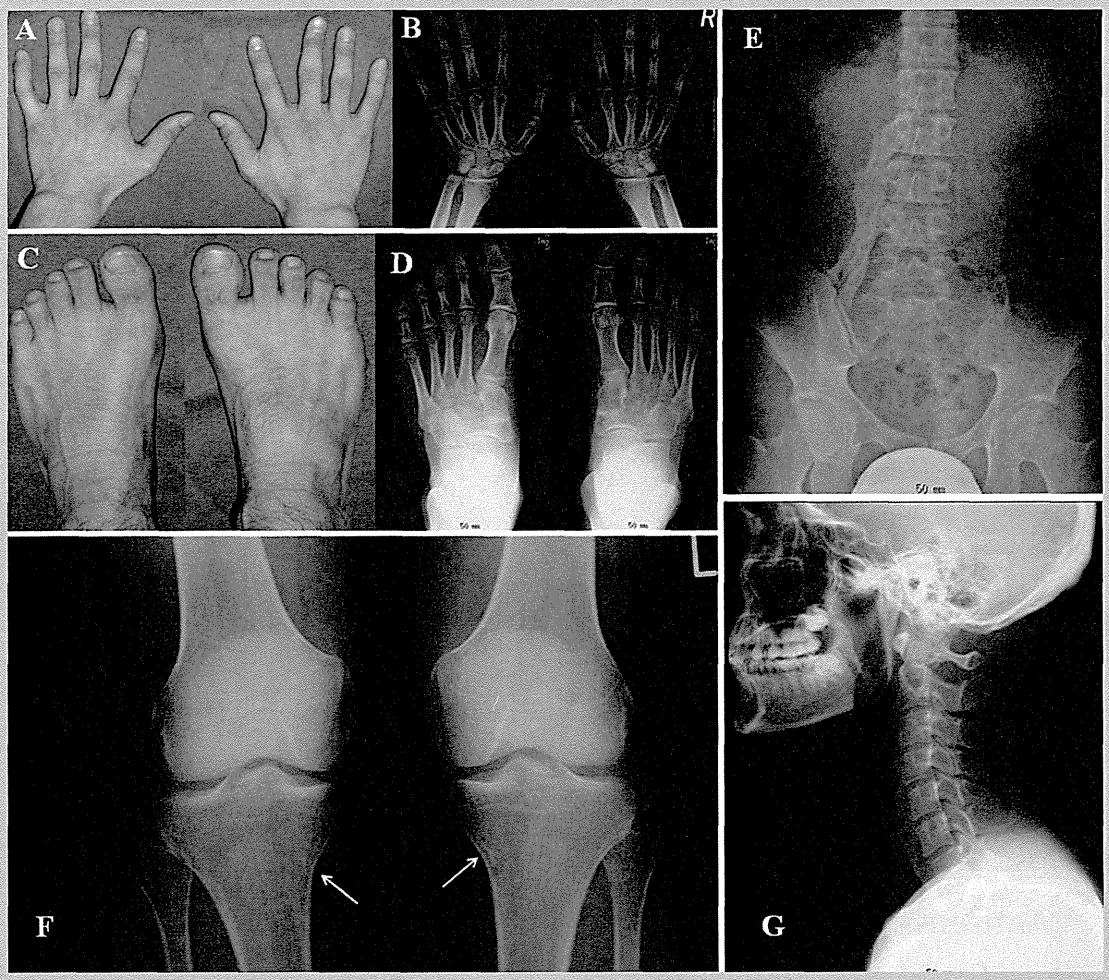

FIG. 2. A,B: Left little finger camptodactyly, slight shortening of the thumbs, and slight shortening of the first metacarpal bones of both hands. C,D: Overall short toes and lack of DIP joint on the fourth and fifth toes of both feet. No malformation of the great toes was seen. E: Bilateral heterotopic ossification in the paraspinal muscles. F: Mild bilateral osteosclerotic lesion in the proximal tibial inner intracortical bone (arrows). G: Cervical spine malformation (C6 spinous process was slightly larger and C6/7 intervertebral joint was narrow).

joint was observed without any prior incident. Although the range of motion improved within two weeks, MRI showed a large T2-high intensity lesion in the right scapular region (subcutis to tunica muscularis) (Fig. 1). He was then referred to our hospital because lumbar heterotopic ossification was still evident. At age 22 years, he had no abnormal facial appearance or trismus. Range of motion in the cervical spine was limited in all directions (flexion 20°, extension 20°, rotation 20°/20°, lateral flexion 30°/30°) and that in the lumbar spine was 30° for both flexion and extension. Range of motion in the upper extremities including the right shoulder joint was normal. With regard to range of motion in the lower extremities, hip abduction and adduction were restricted (30°/30° and 0°/0°, respectively) but other joints were normal. The left little finger showed camptodactyly and thumbs were slightly short (Fig. 2A). The toes were short overall, and the lack of a distal interphalangeal (DIP) joint on the fourth and fifth toes of both feet was observed (Fig. 2C, D). Radiography showed mature heterotopic ossification bilaterally in the lumbar paraspinal muscles (Fig. 2E), mild osteosclerotic lesions bilaterally in the inner cortex of the proximal tibia (Fig. 2F), cervical spine malformation (C6 spinous process is slightly larger and C6/7 intervertebral joint is narrowed) (Fig. 2G), and slight shortening of the first metacarpal bones of both hands (Fig. 2B).

MUTATION ANALYSIS

Informed written consent was obtained from the patient for gene analysis, and genetic diagnosis was performed at the Project of Clinical and Basic Research for FOP at Saitama Medical University. Genomic DNA was extracted using a QIAamp DNA blood kit (Qiagen, Hilden, Germany), and coding of exon 4 in *ACVR1* was amplified by a standard polychromase chain reaction (PCR) method using Pfx platinum DNA polymerase (Invitrogen, Carlsbad, CA). The PCR product purified by a Microcon-100 column (Takara Bio, Shiga, Japan) was directly sequenced using an ABI3500 Genetic Analyzer (Applied Biosystems, Foster City, CA). The following oligonucleotides were used as primers for PCR and DNA sequencing:

5′-CCAGTCCTTCTTCCTTCTTCC-3′ (forward)
5′-AGCAGATTTTCCAAGTTCCATC-3′ (reverse).

RESULTS

Analysis was first performed to verify the R206H (617G>A) mutation, which was not identified. All exons of *ACVR1* were then examined, which led to the identification of the *ACVR1* (587T>C) mutation in exon 6 of *ACVR1* (Fig. 3), the same mutation as that reported by Gregson et al. [2011].

DISCUSSION

To date, FOP can be classified into three phenotypes: classic FOP, FOP-plus (features of classic FOP plus one or more atypical FOP features) and FOP variant. In the past, most typical features of FOP reported were congenital malformations of the great toes and progressive heterotopic ossification within muscle tissues by the age of 10 years [Connor and Evans, 1982; Lin et al., 2006; Shore et al., 2006; Nakajima et al., 2007; Bocciardi et al., 2009; Kaplan et al., 2009; Lee et al., 2009; Ratbi et al., 2010]. Recently, there have been reports of an FOP variant with no malformation of the great toes and relatively delayed onset of heterotopic ossification [Bocciardi et al., 2009; Kaplan et al., 2009; Barnett et al., 2011].

The clinical symptoms of our patient are similar to those reported by Gregson et al., not only with regard to the delayed onset of heterotopic ossification with a slower and mild clinical

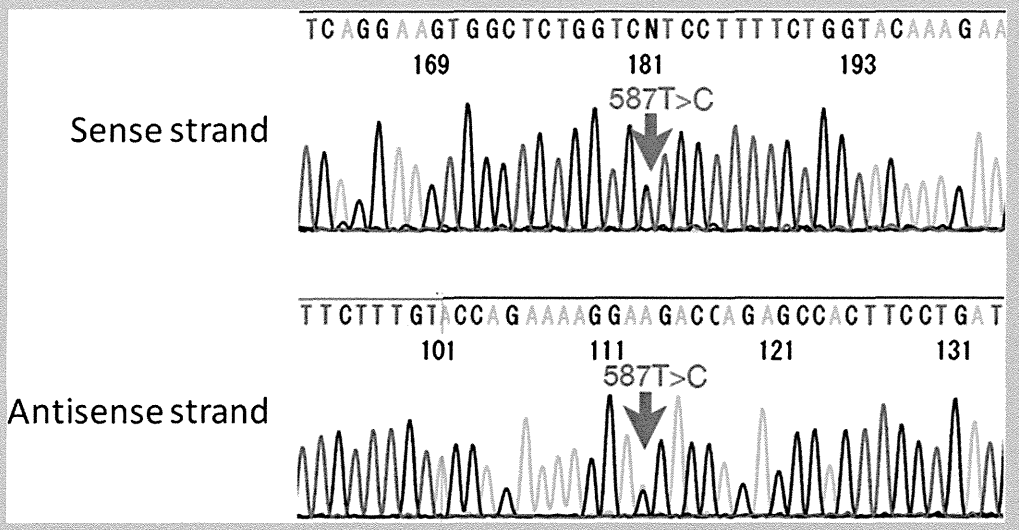

FIG. 3. The 587T>C mutation of *ACVR1*. Analysis by DirectSequence identified the *ACVR1* (587T>C) heterozygous mutation in exon 6 of *ACVR1*.

TABLE I. Comparison Between Our Patient and the First Reported Patient With *ACVR1* (587T>C) Mutation

	Classic FOP	This patient	Gregson et al.
ACVR1 mutation	c.617 G>A	c.587 T>C	c.587 T>C
Codon change	R206H	L196P	L196P
Gender	M, F	M	F
Age of onset (year)	1–10	17	21
Clinical course	Moderate/severe	Slow	Slow
Classic FOP feature			
Malformations of great toe	+	−	−
Progressive HO	+	+	+
Common features in classic FOP			
Proximal medial tibial exostoses	>90%	[b]	−
Cervical spine malformations	>80%[a]	+[c]	+[a]
Short broad femoral necks	>70%	−	−
Thumb malformations			
Short first metacarpal	>50%	+	−
Conductive hearing impairment	>50%	−	−
Additional features			
Little finger camptodactyly		+	+
Short toes		+	−
Absent DIP joints in toes		+	−
Refs.	Kaplan et al. [2009]		Gregson et al. [2011]

Similarities were observed in the clinical course, cervical spine malformations, and little finger camptodactyly.
HO, heterotopic ossification; DIP, distal interphalangeal; −, absent; +, present.
[a]Ossification between the facets joints.
[b]Osteosclerotic lesions suggestive of mild manifestation of exostoses.
[c]Slightly larger spinous process and narrowed intervertebral joint.

course but also with regard to cervical spine malformations as the features of classic FOP and little finger camptodactyly as an additional feature [Gregson et al., 2011] (Table I). The similarity of symptoms in these two patients, along with the same location of mutation *ACVR1* (587T>C) determined by gene analysis, suggests the relationship between clinical features, age of onset and location of the mutation [Kaplan et al., 2009]. However, certain different features were observed in our patient: cervical spine malformations (a slightly larger spinous process and a narrower intervertebral joint); mild osteosclerotic lesions bilaterally in the proximal tibial inner cortex, but less pronounced than proximal tibial exostoses; malformations of the fingers (little finger camptodactyly and slight shortening of the first metacarpal bones of both hands) and toes (overall shortening of the toes, and bilateral lack of DIP joint on the fourth and fifth toes).

ACVR1 (587T>C) is not registered in the SNP databases including Japanese data. A recent study has found that mutant ACVR1 (L196P) of *ACVR1* (587T>C) have been identified as a gain-of-function mutation, the same as mutant ACVR1 (R206H) of that in classic FOP. It is also reported that in vitro activities, mutant ACVR1 (L196P) are higher than those of other mutant ACVR1 (G356D) of a variant FOP, and equivalent to those of mutant ACVR1 (R206H) of the typical FOP. Meanwhile, differences from the clinical features of classic FOP, such as absence of great toe malformation and delayed onset of heterotopic ossification in muscle tissue, suggest the possibility that the activities of mutant ACVR1 (L196P) may be suppressed in vivo by some mechanism [Ohte et al., 2011].

It has become evident that the location of mutation in FOP patients may differentiate the clinical features between typical and atypical FOP. This report on a second patient with *ACVR1* (587T>C) mutation worldwide is particularly significant in that it highlights the differences between clinical symptoms of the first reported patient with *ACVR1* (587T>C) mutation and those of classic FOP. Accumulating data on novel mutations is important for evaluating pathology and establishing treatments and for helping future studies to clarify the in vivo mechanisms of *ACVR1* (587T>C) and its relationship with other mutation types.

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